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### Eosinophilia during Psoriasis Treatment with TNF Antagonists

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#### Key Words

Psoriasis vulgaris · Eosinophilia · Tumour necrosis factor  $\alpha$  · Adalimumab · Etanercept

#### Introduction

Psoriasis is dependent on Th1- and Th17-polarized CD4 T cells that produce pro-inflammatory cytokines (such as TNF- $\alpha$ ) and thus prompt the development of acanthosis and papillomatosis [1]. Blocking TNF- $\alpha$  greatly improves clinical outcomes [2, 3] and results in fewer (and generally milder) side effects than observed for older drugs (e.g. cyclosporin A or methotrexate). Common side effects are temporary headaches, nasopharyngitis, upper respiratory tract infections, injection site reactions, eczema and (more rarely) vasculitis [4]. Here, we report on 3 patients with psoriasis (variously with and without joint involvement) who developed isolated eosinophilia during TNF blockade.

#### Patient 1

A 46-year-old Caucasian male with a 30-year history of severe psoriasis and psoriatic arthritis was treated with a combination of adalimumab, anthralin and topical steroids. Prior to treatment, slight eosinophilia had been noted (730/ $\mu$ l of blood, relative to an upper normal limit of 700/ $\mu$ l). The serum tryptase level was normal (<11.7 U/l). The patient had a history of seasonal allergic rhinitis but no other signs of atopy. Total IgE was <100 kU/l. Prior to initiation of adalimumab treatment, the patient had a Psoriasis Area and Severity Index (PASI) score of 11.3, which fell to 0.1 after 4.5 months of treatment. After 3.25 months of therapy, he developed eosinophilia (1,550/ $\mu$ l; fig. 1a). Eosinophilic cationic protein (ECP) was also elevated (38.20  $\mu$ g/l; normal range 1.8–13.3  $\mu$ g/l). A parasite screen was negative, and total IgE levels remained normal. No signs of a haematological disorder were found. The patient also reported transient urticarial skin changes that developed after the onset of adalimumab treatment but had resolved before clinical examination. After discontinuation of adalimu-

mab, ECP levels and eosinophil counts fell to normal values within 5 months. However, the PASI increased to 10.1. Etanercept was introduced, and the eosinophil count was still in the normal range 3 months later.

#### Patient 2

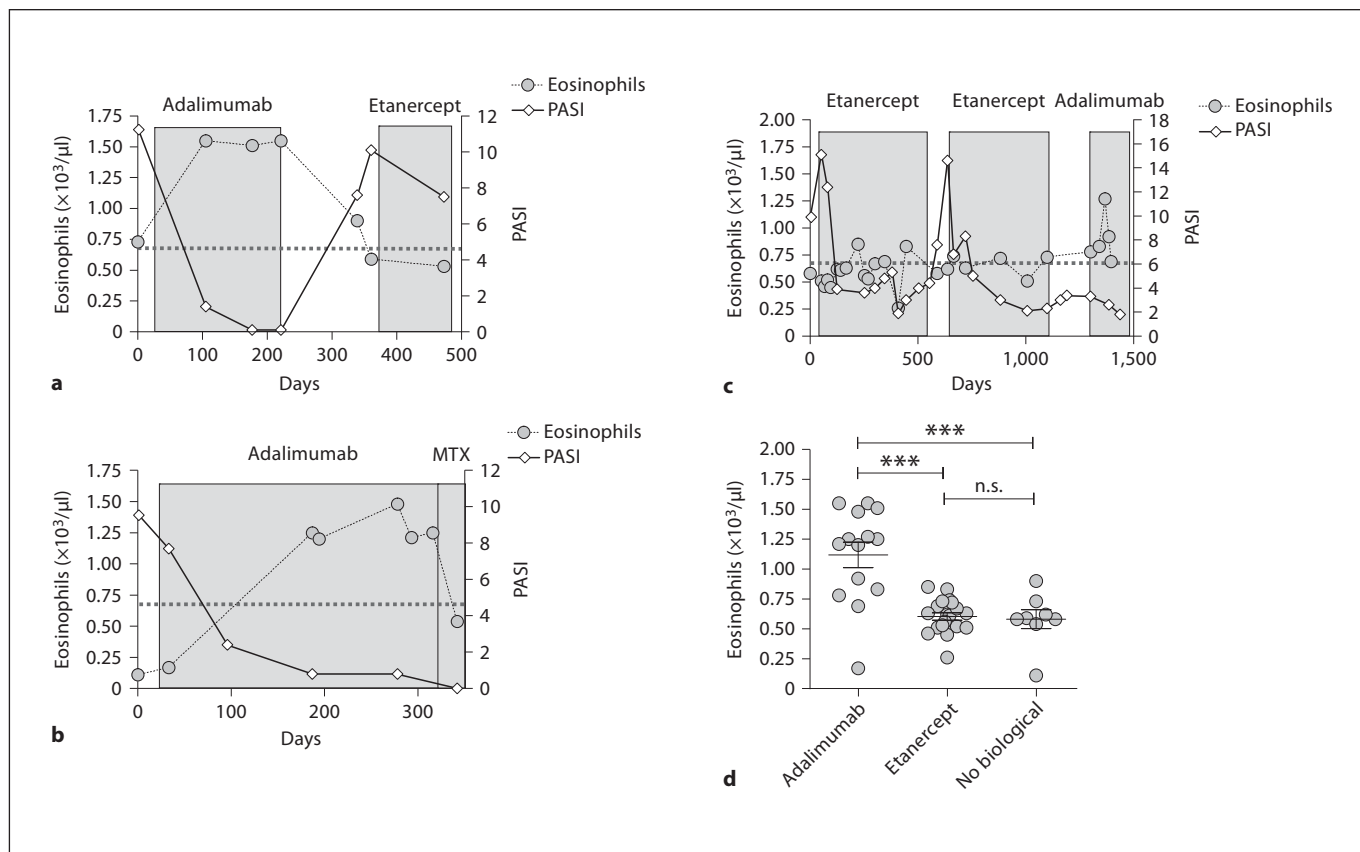
A 55-year-old Caucasian female with a 13-year history of plaque-type psoriasis and psoriatic arthritis had failed to show satisfactory results after receiving anthralin, topical steroids, calcineurin inhibitors, narrow-band UVB and psoralen + UVA. Combination treatment with adalimumab, anthralin and topical steroids was initiated. The complete blood count was normal. Over the next 11 months, the PASI fell from 7.7 to 0. After 8.5 months of therapy, she developed eosinophilia (1,250/ $\mu$ l, peaking at 1,480/ $\mu$ l; fig. 1b). After 3.5 months, ECP was elevated (149  $\mu$ g/l). A parasite screen of a faecal specimen revealed asymptomatic colonization with the facultative pathogen *Dientamoeba fragilis*, which we decided not to treat [5]. The total blood IgE level was not elevated, and tryptase was slightly elevated (14.7 U/l). The haematological profile was normal. After a switch from adalimumab to methotrexate, the eosinophilia resolved within 10 days.

#### Patient 3

A 24-year-old Caucasian male had been consulting us for phototherapy- and isotretinoin-resistant plaque psoriasis without joint involvement for 11 years. He had an atopic disposition and a history of resolved hepatitis C. With 2  $\times$  25 mg etanercept per week, the PASI fell from 15.1 to 1.9 within a year. During the first course of treatment, above-normal eosinophil counts >700/ $\mu$ l alternated with normal values (fig. 1c). At a value of 830/ $\mu$ l, treatment was temporarily withdrawn, and the eosinophil count normalized. When etanercept was re-introduced, low-level eosinophilia recurred (740/ $\mu$ l). During subsequent treatment with adalimumab, however, the eosinophil count rose up to 1,270/ $\mu$ l and then spontaneously resolved to values at the upper limit of the normal range (690/ $\mu$ l). No clinical findings were associated with these fluctuations of eosinophil counts other than the temporal association with the TNF- $\alpha$  antagonists. A parasite screen was normal. Total IgE levels were elevated (360 kU/l), as was ECP. The SX1 inhalant allergen screen was positive. Serum tryptase was not elevated. The haematological profile was normal. An overview of the clinical data of all 3 patients is shown in table 1. Eosinophils were significantly increased during treatment with adalimumab compared to treatment with etanercept or no biological agent (fig. 1d).

#### Discussion

The introduction of biologicals has improved treatment efficacy in several chronic inflammatory disorders. Early identifica-



**Fig. 1. a–c** Changes in eosinophil count and PASI values over time, for patients 1, 2 and 3, respectively. Grey boxes indicate the periods of treatment with biologics or methotrexate (MTX). The dashed line shows the cut-off value of the eosinophilia (700/μl). **d** Scatter plot of eosinophil numbers measured during adalimumab versus etanercept treatment versus no treatment. \*\*\*  $p < 0.001$ ; n.s. = non-significant.

tion and reporting of potential drug-related side effects is an important task for clinicians. However, deviations from normal laboratory values must be interpreted in a clinical context, and not all changes are necessarily of clinical relevance. Here, we report 3 cases of eosinophilia that were temporally associated with the administration of TNF antagonists. In 1 of 3 patients, eosinophilia resolved spontaneously during adalimumab treatment. Two patients developed de novo eosinophilia, and 1 patient's pre-existing eosinophilia worsened. Some cases of eosinophilic pathology associated with TNF- $\alpha$  inhibitors have been observed before. Some cases of eosinophilic pathology associated with TNF- $\alpha$  inhibitors have been observed before. Etanercept-induced eosinophilic, cellulitis-like reactions and the development of Wells syndrome during adalimumab administration have been described [6, 7]. Comparable to our observation, Boura et al. [6] showed that the eosinophil pathology was associated with adalimumab. In addition, a patient with no history of atopy developed asthma during adalimumab therapy [8]. Vester et al. [9] reported a woman suffering from acrodermatitis continua of Hallopeau who had been treated with adalimumab and developed a transient blood eosinophilia. Moreover Cancelliere et al.

[10] could show a connection between infliximab and etanercept administration and eosinophilia in a female patient treated for rheumatoid arthritis. The patient also developed clinical symptoms in terms of a subacute prurigo [10].

Eosinophilia is stated as a less common side effect (<1%) in the product monograph of adalimumab (Humira®) without providing further information on the severity or association with other clinical or serological findings [11]. In the eHealthMe database, eosinophilia has been observed during adalimumab treatment in 0.07% of reported side effects [12]. The majority of patients were in the 3rd or 5th decade, most of them were female and in about 80% the development of eosinophilia occurred within the first 2 years of treatment [12]. Psoriasis was not in the top underlying conditions of these patients, and there was no information about the severity of eosinophilia [12].

We could not identify any other apparent explanation for the 3 patients' elevated eosinophil counts. There were no relevant parasitological infections or haematological disorders. Two patients (No. 1 and 3) had an atopic predisposition (albeit mild) that alone would have been unlikely to cause eosinophilia. Patient 1 developed severe eosinophilia after the introduction of adalimumab;

**Table 1.** Clinical data of patients 1–3

	Patient 1	Patient 2	Patient 3
Gender	male	female	male
Age, years	46	55	24
Disease duration, years	30	13	11
Psoriatic arthritis	yes	yes	no
Atopy	yes	no	yes
Biological used	adalimumab, etanercept	adalimumab	etanercept, adalimumab
PASI before treatment with a biological	11.3	7.7	15.1
Trough PASI during treatment	0.1	0	1.9
Reached PASI <sub>75</sub>	yes	yes	yes
Peak eosinophil count, $\times 10^3/\mu\text{l}$	1.55	1.48	1.27
Worsening of psoriasis during eosinophilia	no	no	no
Other symptoms or skin changes during eosinophilia	urticaria	no	no
Discontinuation/change of biological	yes	yes	yes
Improvement of eosinophilia after discontinuation	yes	yes	yes
Treatment switch	etanercept	methotrexate	adalimumab
Pathological results by haematologist	no	no	no
Parasitology	negative	<i>Dientamoeba fragilis</i>	negative
Total IgE, kU/l	54.6	24.6	360
Elevated ECP	yes	yes	yes
Elevated tryptase	not determined	yes	no

the condition resolved after discontinuation. Patients 2 and 3 did not have eosinophilia prior to therapy. Patient 2 developed eosinophilia after the administration of adalimumab. After the withdrawal of adalimumab, the patient's haematological parameters returned to normal values. Patient 3 also developed low-grade eosinophilia after the administration of etanercept. During a treatment-free interval, the eosinophilia disappeared and then recurred after the re-introduction of etanercept. After a switch to adalimumab, the eosinophil count rose even higher initially and then spontaneously normalized.

The mechanism of TNF inhibition leading to eosinophilia remains unclear. The generation of IgE-class-switched antibodies might lead to IgE-mediated drug hypersensitivity and subsequent eosinophilia [13, 14]. Furthermore, TNF antagonism might induce an immune deviation from the Th1 cytokine pattern of psoriasis to the Th2 phenotype [15], which can lead to eosinophilia and elevated IgE levels [16]. Quaglini et al. [15] could show that patients suffering from psoriasis present an up-regulation of Th1 and Th17 in the peripheral blood and a down-regulation of regulatory T cell subsets at baseline. Patients responding to etanercept administration showed a significant reversal of the Th1/Th17 activation indicated by a downmodulation in the mRNA expression of the hallmark target genes and cytokines Stat-3/IL-23p19 and Stat-4/IL-12p35, and a concomitant upregulation of Th2 and regulatory T cell subsets as shown by GATA-3, Foxp3/IL-2 and circulating CD4+CD25+ bright FoxP3+ T cell subsets in all responsive patients [15]. This data showed the potential involvement of CD4+ T cell modulation in the mechanisms of response induction triggered by etanercept and possibly other TNF inhibitors. CD4+ T cell modulation can be effective in reversing the psoriatic phenotype, as Ghoreschi

et al. [17] showed with IL-4 therapy in psoriatic patients that induced a marked clinical improvement by upregulation of IL-4-producing CD4+ T cells.

The Th1-Th2 balance shift might be the reason that during TNF antagonism eosinophilia and PASI showed a reciprocal relationship as seen in figure 1a–c. The more effective and sustained the inhibition was, the stronger the eosinophilia. Thus, in some patients a pronounced TNF- $\alpha$  blockade may amplify an immune deviation to the Th2 phenotype [18]. Although we did not assay serum levels of IL-5 in the isolated cases described here, in the future we shall screen for any potential elevation of this cytokine [19]. TNF- $\alpha$  inhibitors might also be able to influence eosinophil apoptosis. Mature eosinophils have a lifespan of only 3–5 days and are then eliminated by apoptosis [20, 21]. The observation that adalimumab induced more pronounced effects than etanercept might reflect adalimumab's higher potential to reduce the PASI and therefore a stronger shift to Th2. Furthermore, different structural properties of both drugs may also play a role. Infliximab for example as a monoclonal antibody (but not etanercept) has been shown to induce apoptosis in lamina propria T lymphocytes in Crohn's disease [22]. Thus, the group of TNF- $\alpha$  antagonists is heterogeneous, and our findings might express this circumstance.

In general, TNF- $\alpha$  antagonists have been found to have differential effects on haematopoiesis. A psoriasis patient treated with infliximab developed severe neutrophilia [23]. In a study on chronic anaemia of patients with inflammatory bowel disease, 18 of 27 patients undergoing treatment with infliximab were anaemic; most of them had anaemia of chronic disease. Infliximab reduced disease activity and improved anaemia in 12 patients. This was mediated by an increased production of erythropoietin for the

degree of anaemia. In vitro infliximab increased the growth of erythroid progenitors from the peripheral blood of patients with active disease [24]. Global analysis of haemoglobin levels of 5 phase III trials for Crohn's disease (CHARM trial), rheumatoid arthritis (ATTRACT, ASPIRE and START trials) and ankylosing spondylitis revealed significant improvement of anaemia by infliximab and adalimumab [25–27]. Etanercept has even been used as a successful salvage treatment in severe aplastic anaemia [28].

On the other hand, blocking TNF- $\alpha$  can also have myelosuppressive effects. Infliximab has been used on a series of myelodysplastic patients with partial success [29]. Etanercept led to aplastic anaemia complicated by sepsis in a patient with rheumatoid arthritis [30].

Infliximab produced severe neutropenia in a patient with rheumatoid arthritis, and rechallenge with infliximab as well as etanercept led to the same effect, arguing for a class effect in the respective patient [31]. Another report concerned infliximab-induced thrombocytopenia and neutropenia [32]. Adalimumab led to neutropenia in 2 cases [33, 34], in 1 instance associated with expansion of the T-large granular lymphocyte compartment [34].

Taken together, eosinophilia is a rare side effect of anti-TNF- $\alpha$  treatment. These case reports underline the importance of the early identification and reporting of potentially drug-induced adverse events. Side effects such as isolated eosinophilia are not clinically detectable but can potentially lead to severe organ damage caused by the release of toxic granule proteins (such as eosinophil-derived neurotoxin, ECP, eosinophil peroxidase and eosinophil major basic protein) [35]. This should be taken into account when persistent eosinophilia is identified during TNF- $\alpha$  inhibition.

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